gional NMR Facility. In addition, we wish to thank the Johnson-Matthey Corp. for a generous gift of palladium chloride.

Supplementary Material Available: Representative experimental procedures, characterization data, and full spectral and analytical data for compounds **8-19** (8 pages). Ordering information on any current masthead page.

Synthesis and Rearrangement of Methanesulfonate Esters of *N*-Hydroxyacetanilides. A Model for a Penultimate Carcinogen

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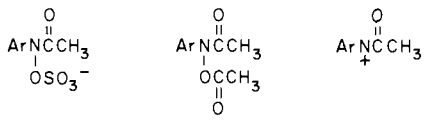
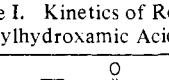
Extensive studies[2] indicate that the extreme carcinogenicity of certain arylamines is due to metabolic conversions that result in the formation of sulfate[2] or acetate[3] esters of hydroxamic acids, such as **1** and **2**, respectively, which then ionize to form the



1 **2** **3**

acylarylnitrenium ion **3** as the ultimate electrophilic carcinogen.[2,4] Unfortunately, relatively little evidence exists for the heterolytic cleavage of the sulfonate esters of *N*-arylhydroxamic acids, primarily because previous attempts to prepare this class of compounds have led mostly to materials with rearranged structures.[5,6] We now wish to report on the synthesis, isolation, and characterization of a series of methanesulfonate esters of monosubstituted *N*-arylhydroxamic acids. We have demonstrated, through a classical Hammett $\sigma^+\rho$ study that cleavage of the N-O bond of these esters occurs in a heterolytic manner with $\rho = -9.24$.

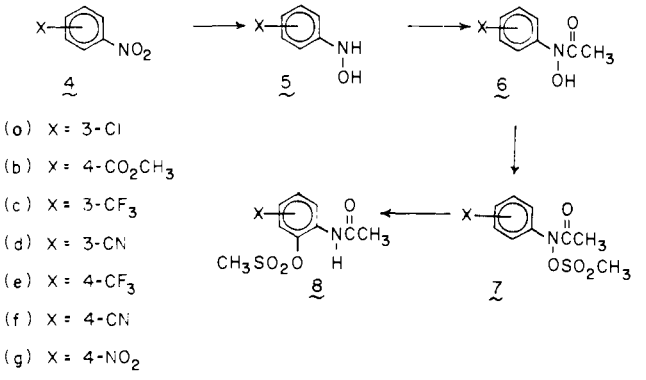
Table I. Kinetics of Rearrangement of Monosubstituted *N*-Arylhydroxamic Acid *O*-Methanesulfonates in Chloroform-d_1



X	$k_{25\,°C}$, s^{-1} [a]	k_{rel}	σ^+
7a, X = 3-Cl	1.31×10^{-4}	2690	0.399
7b, X = 4-CO_2CH_3	3.33×10^{-5}	684	0.489
7c, X = 3-CF_3	1.84×10^{-5}	378	0.520
7d, X = 3-CN	1.95×10^{-6}	40	0.562
7e, X = 4-CF_3	1.41×10^{-6}	29	0.612
7f, X = 4-CN	4.05×10^{-7}	8	0.659
7g, X = 4-NO_2	4.87×10^{-8}	1	0.790

[a] Rates extrapolated from higher temperatures. Kinetics were measured at 40-110 °C.

In a general procedure, the appropriate substituted nitrobenzene derivatives, **4**, were reduced to the corresponding *N*-arylhydroxylamines, **5**, with zinc dust, ammonium chloride, and aqueous ethanol.[7,8] Treatment of **5** with acetyl chloride in ether with an aqueous sodium bicarbonate second phase at 0 °C gave **6a-f**.[8-10] For the preparation of **6g**,[8] it was necessary to use a



(a) X = 3-Cl
(b) X = 4-CO_2CH_3
(c) X = 3-CF_3
(d) X = 3-CN
(e) X = 4-CF_3
(f) X = 4-CN
(g) X = 4-NO_2

two-step procedure, which involved bisacetylation of **5g** followed by removal of the *O*-acetyl group through transesterification with methanol in 41% overall yield. The hydroxamic acids **6a-g** were converted into the corresponding sulfonates, **7a-g**,[8] by reaction with methanesulfonyl chloride and triethylamine in methylene chloride below 0 °C (**7a-d**) or below 25 °C (**7e-g**).

The thermal rearrangements of **7a-g** were measured in chloroform-d_1 and were followed by ^1H NMR by monitoring the disappearance of the mesylate methyl group of **7** and the appearance of a new mesylate methyl group for the *internal return product*.[11] Table I lists the rates of rearrangement that were observed. All rate studies were followed for at least three half-lives and showed excellent pseudo-first-order kinetics. Application of the Hammett equation showed that the rate data correlated excellently with σ^+ and gave $\rho = -9.24$ ($r = 0.984$). This exceptionally large ρ leaves little doubt that the N-O bonds of sulfonate esters of *N*-arylhydroxamic acids undergo facile heterolytic cleavage, even in relatively nonpolar solvent environments such as chloroform. In all cases the product was that of internal return to the ortho position of the aryl moiety of the acetanilide.[12]

(1) Deceased September 2, 1983.
(2) Kriek, E.; Westra, J. G. In "Chemical Carcinogens and DNA"; Grover, P. L., Ed.; CRC Press: Boca Raton, FL, 1979; Vol. 2, pp 1-28. Miller, J. A.; Miller, E. C. *Prog. Exp. Tumor Res.* **1969**, *11*, 273. Scribner, J. D.; Miller, J. A.; Miller, E. C. *Cancer Res.* **1970**, *30*, 15. Miller, J. A. *Ibid.* **1970**, *30*, 559. Suss, R.; Kinzel, U.; Scribner, J. D. "Cancer Experiments and Concepts"; Springer-Verlag: New York, 1973; pp 22-42. Cramer, W. J.; Miller, J. A.; Miller, E. C. *J. Biol. Chem.* **1960**, *235*, 885. Weisburger, J. H.; Weisburger, E. K. *Pharmacol. Rev.* **1973**, *25*, 1. See also: Miller, E. C. *Cancer Res.* **1978**, *38*, 1479. Scribner, J. D. *J. Org. Chem.* **1976**, *41*, 3820. Miller, E. C.; Miller, J. A. *Cancer* **1981**, *77*, 2327. Ford, G. P.; Scribner, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 4281. DeBaun, J. R.; Rowley, J. Y.; Miller, E. C.; Miller, J. A. *Proc. Soc. Exp. Biol. Med.* **1968**, *129*, 268. Weisburger, J. H.; Yamamoto, R. S.; Williams, G. M.; Grantham, P. H.; Matsushima, T.; Weisburger, E. K. *Cancer Res.* **1972**, *32*, 491.
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(8) All compounds reported gave spectral data consistent with the assigned structures. Satisfactory exact mass molecular weights and/or elemental analyses were obtained on all new compounds.
(9) Gupta, V. K.; Tandon, G. *J. Indian Chem. Soc.* **1969**, *46*, 831.
(10) Yields varied from 28% to 80%.
(11) The chemical shift of the mesylate methyl group of **7** varied from δ 3.04 to 3.13. The chemical shift of the mesylate methyl group of **8** varied from δ 3.29 to 3.41 (1,2,4-trisubstituted acetanilides), δ 3.38 to 3.53 (1,2,3-trisubstituted acetanilides), and δ 3.20 to 3.31 (1,2,5-trisubstituted acetanilides).

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In summary, the data presented above indicate the great propensity that exists for heterolytic cleavage of the N–O bond of suitably derivatized *N*-arylhydroxamic acids. It provides a solid basis for the proposal that sulfate esters of *N*-arylhydroxamic acids can ionize to produce acylarylnitrenium ions as the ultimate carcinogens derived from certain aromatic amines.

Acknowledgment. We are indebted to the National Cancer Institute and to the Institute of General Medical Sciences of the National Institutes of Health for grants that supported this investigation.

Registry No. 4a, 121-73-3; **4b**, 619-50-1; **4c**, 98-46-4; **4d**, 619-24-9; **4e**, 402-54-0; **4f**, 619-72-7; **4g**, 100-25-4; **6a**, 88730-41-0; **6b**, 62641-35-4; **6c**, 88730-42-1; **6d**, 80584-66-3; **6e**, 88730-43-2; **6f**, 80584-65-2; **6g**, 67274-52-6; **7a**, 88730-34-1; **7b**, 88730-35-2; **7c**, 88730-36-3; **7d**, 88730-37-4; **7e**, 88730-38-5; **7f**, 88730-39-6; **7g**, 88730-40-9.

(12) Product yields[8] were determined by HPLC analysis vs. an internal standard. The yields were as follows: **8a**, 100% (29:71 ratio of 1,2,3- to 1,2,5-substitution); **8b**, 86%; **8c**, 100% (45:55 ratio of 1,2,3- to 1,2,5-substitution); **8d**, 100% (46:54 ratio of 1,2,3- to 1,2,5-substitution); **8e**, 87%; **8f**, 96%; **8g**, 96%. All products were stable to the reaction conditions.

Transfer of Hydrogen from Carbon–Hydrogen Bonds. Synthesis, Structure, and Reactions of 1,3,5-Triphenyl-2,4,6-trithia-1,3,5-tristannaadamantane

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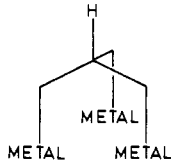
Many important redox reactions involve the formal transfer of hydride from a carbon–hydrogen bond.[2,3] Compounds in which a carbon–hydrogen bond is adjacent to several carbon–metal bonds should be especially reactive,[3b] since loss of hydride or hydrogen may yield a cation or radical stabilized by hyperconjugation.[4,5] Loss of hydrogen is fastest when the carbon–hydrogen and carbon–metal bonds are antiperiplanar,[6] so the best donors should resemble structure **1**. The first synthesis of a compound of this



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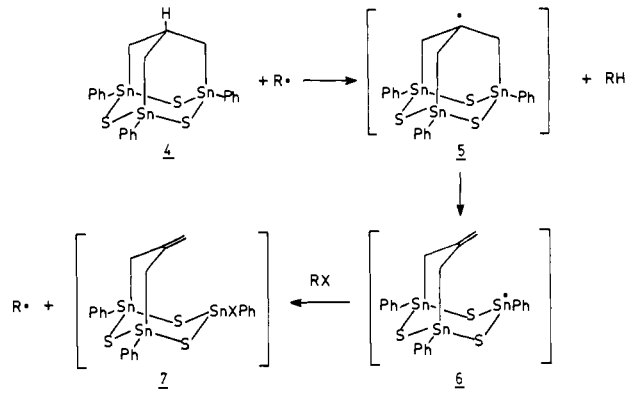
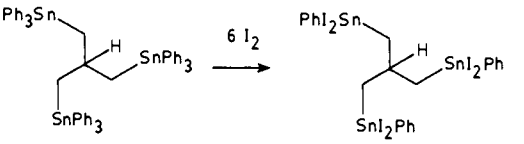
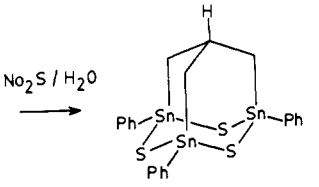
kind and the unusual reactivity of its central carbon–hydrogen bond are described below.

Scheme I







Treatment of tris[(triphenylstannyl)methyl]methane (**2**)[3b] with 6 equiv of iodine cleanly produced hexaiodostannane **3**. Aqueous sodium sulfide converted this intermediate into 1,3,5-triphenyl-2,4,6-trithia-1,3,5-tristannaadamantane (**4**)[7,8] in 79% overall yield. The large coupling between the bridgehead hydrogen and tin ($^3J(^{119}Sn,H)$ = 206.5 Hz)[9] confirmed that all three carbon–tin bonds were antiperiplanar to the central carbon–hydrogen bond. The long tin–sulfur bonds (2.41 Å)[10] were expected to introduce a significant element of strain, and X-ray crystallographic study of compound **4** has shown that the bridgehead carbon is severely flattened as a result.[11]

In chloroform at 25 °C, stannaadamantane **4** reduced triphenylcarbenium hexafluorophosphate to triphenylmethane in 83% yield. Unlike the very slow reduction of triphenylcarbenium by tris[(triphenylstannyl)methyl]methane (**2**),[3b] reduction by stannaadamantane **4** is almost instantaneous. More impressive is the observation that stannaadamantane **4** reduces alkyl halides to the corresponding hydrocarbons. For example, when α-bromo-*p*-phenylacetophenone (27 μmol) was warmed with compound **4** (30 μmol) and AIBN (16 μmol) in benzene (1.5 mL, 75 °C, 3 h), *p*-phenylacetophenone was formed in 48% yield.[12] In general, iodides are reduced fastest, followed by bromides and then

(1) Fellow of the Natural Sciences and Engineering Research Council of Canada.

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(12) Yields measured by NMR were nearly quantitative. We attribute the moderate isolated yields to the extremely small scale of our preparative reactions.

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